ATTACHMENT B
Amendments to the Claims

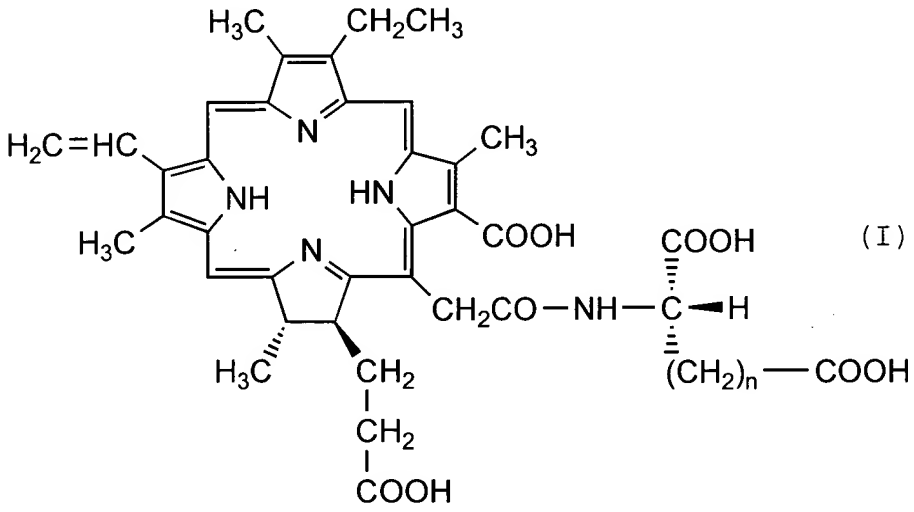
This listing of claims will replace all prior versions, and listings, of claims in the application.

1. Canceled.

2. Canceled.

3. (Currently Amended) A photodynamic therapy method of suppressing thickening of vascular intima in a blood vessel wall and vascular restenosis of the blood vessel which are inducible after angioplasty treatment of the blood vessel has been done for a purpose of dilating the stenosed site of the blood vessel, said method comprising:

~~administering mono-L-aspartylchlorin e6 or mono-L-glutamylchlorin e6 of the general formula (I)~~



~~wherein n is 1 or 2~~ before or after the angioplasty treatment, intravenously administering a photosensitizing compound selected from the group consisting of mono-L-aspartylchlorin e6, ~~or~~ and a salt thereof, to a patient whose blood vessel has received treatment by angioplasty;

making the administration of ~~the compound of the formula (I) at a dosage~~ the photosensitizing compound only one time at a dosage of 0.1-5 mg/kg of body weight so ~~adjusted~~ that ~~a therapeutically effective amount of~~ the photosensitizing compound ~~of formula (I)~~ can accumulate in the cell layers of the blood vessel wall at the site of the blood vessel having received the treatment by angioplasty;

inserting percutaneously and transluminally into and locating in the interior of said blood vessel at a position of a site thereof having received the treatment by angioplasty, a laser-irradiating device that comprises a balloon catheter having a central and longitudinal hole therein and having an inflatable balloon made of a laser-transmissive material at a front end of said catheter and that comprises a laser-irradiating optical fiber so arranged as to extend within and through said central and longitudinal hole in the balloon catheter and is equipped on the catheter with an inlet tube for introduction of an inflating liquid to be sent into an interior space of said inflatable balloon; and adjusting the position of the balloon catheter within the blood vessel so that said balloon of the balloon catheter is located oppositely to the angioplasty-treated site of the blood vessel;

making said balloon of the balloon catheter inflate by delivery of the inflating liquid in the interior space of the balloon of the catheter via said inlet tube for introduction of the inflating liquid into the balloon interior space of the catheter of said

device, thereby to produce an inflated balloon in the balloon catheter;

allowing a central axis of the laser-irradiating optical fiber present within the central and longitudinal hole of said balloon catheter to be held coincidently with and in the same position as the central axis of the vascular lumen of the blood vessel at the angioplasty-treated site of the blood vessel, with aid of a supporting force which is generated by said inflated balloon and is exerted on the balloon catheter and on the inner wall of the blood vessel at said angioplasty-treated site, with the supporting force maintaining said inflated balloon in tight contact with the inner wall of the blood vessel at the treated site, so as to intercept the bloodstream to be flown between the inflated balloon and the inner wall of the blood vessel at the treated site;

and ~~irradiating the compound of formula (I)~~ at a time point of 0.5-6 hours after the administration of photosensitizing compound, irradiating the photosensitizing compound having accumulated in the interior of the blood vessel wall positioned at the angioplasty-treated site of the blood vessel, with a laser light of ~~an appropriate wavelength~~ 664 nm wavelength at laser fluence of 1 to 10 J/cm^2, by transmitting from a laser-generator the laser light via said optical fiber in the balloon catheter, in a manner that the transmitted laser light is emitted outwardly from the laser-emitting part at the front end of said optical fiber and is made to pass through the liquid medium present in the inflated balloon and through the wall material of said inflated balloon of the balloon catheter which is in tight contact with the inner wall of the blood vessel, so that the emitted laser light irradiates the photosensitizing compound ~~of formula (I)~~ present in the blood vessel inner wall, whereby said compound so irradiated is photoactivated and allowed to generate and exert the suppressive effects thereof against the thickening of

the vascular intima in the angioplasty-treated site of the blood vessel.

4. (Original) The photodynamic therapy method according to Claim 3, wherein the angioplasty is a percutaneous transluminal coronary angioplasty or a percutaneous transluminal angioplasty.

ATTACHMENT C
Detailed Discussion

The following is a detailed discussion addressing issues raised by the Examiner in the Final and First Office Action to supplement the Remarks of this Amendment.

In the Office Action of October 12, 2005 (hereinafter the "Final Office Action"), the Examiner states in the paragraph bridging between pages 2 and 3 of this Action as follows:

> "In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combination of references. See In re Keller, 642 F.2d 413,208 USPQ 871 (CCPA 1981); ..... Here it the obviousness is based on the combined teachings of the references and how it is interpreted by one of ordinary skill in the art. Accordingly, arguing the shortcomings of one does not overcome the obviousness analysis."

Further, in the prior Office Action (mail-dated September 22, 2004, hereinafter the "First Office Action"), the Examiner has stated in the first and second paragraphs at page 7 of the first Office Action as follows:

> "The teachings of Aizawa are described above. Aizawa also teaches the use of Npe6 during an intravascular catherization procedure, wherein the Npe6 are administered locally to the atherosclerotic lesion of interest in the intima of the blood vessel and subsequently the region is exposed to laser beams to provide therapeutic effects (see col 21, line 60-col 26, line 20). Aizawa fails to specifically describe the same method during a percutaneous Transuluminal Coronary Angioplasty procedure (PCTA).
> Narciso teaches that photodynamic therapy is also effective during PCTA procedure to limit restenosis of a blood vessel intima subject to a smooth cell proliferation (see abstract). Narciso specifically explains that the use of a photodynamic agent can be during , before or after a PCTA procedure (see col 2, lines 6-65).

In order to determine whether or not the Examiner's reasonings in the Final Office Action is correct, Applicants have reviewed Aizawa and Narciso, to appreciate fully what are actually disclosed and taught by Aizawa and Narciso.

Clearly from claim 1 of, Aizawa teaches a photodynamic therapeutic method of treating atherosclerosis in the mammalian blood vessel, which method comprises administering to the mammalian host an atherosclerosis-inhibiting effective amount of the Aizawa's fluorescent tetrapyrrole compound (eg., NPe6) that can accumulate selectively (see column 17, lines 56--62 Aizawa) in the atherosclerotic lesion or plaque (composed of cholesterol, lipid material, foam cell, lipophages and proliferating smooth muscle cells (SMC); present in the blood vessel of the mammalian host, and then applying light of sufficient wavelength and sufficient intensity to produce a cytotoxic effect (by the cytotoxic singlet oxygen as formed from the photo-activated photosensitive tetrapyrrole compound; see Aizawa column 16, lines 13-22, on the atherosclerotic lesion or plaque, wherein the application of such light to the lesion or plaque just means the irradiation of the atherosclerotic lesion or plaque with the light or laser capable of photo-activating the photosensitive tetrapyrrole compound having accumulaed selectively within the atherosclerotic lesion or plaque.

Thus, Aizawa is directed exclusively to the photodynamic therapy of atherosclerosis in mammals, but does nowhere allude to and any photodynamic therapy for treating such restenosis in mammalian blood vessels that would be inducible after an angioplasty procedure such as PTCA or PTA for dilating or widening the stenosed site present in a mammalian blood vessel.

The photodynamic therapy of the atherosclerosis disclosed by Aizawa is therefore, clearly distinct from the angioplasty treatment such as the Percutaneous Transluminal Coronal Angioplasty (PTCA) or Percutaneous Transluminal Angioplasty (PTA) that in mechanically injure of the vascular inner wall and the vascular intima of the

blood vessel during PTCA and PTA treatment (see column 1, lines 18-52 of Narciso) often, the mechanical injury may lead to the risk the restenosis of the blood vessel inducible by the angioplasty treatment of the stenotic blood vessel.

The photodynamic therapy of the atherosclerosis usually does not involve any mechanical injury in the vascular inner wall and the vascular intima of blood vessel and is thus free from the problem of vascular restenosis that is inducible by the same biological mechanisms as those occurring during the injury at the angioplasty treatment site of the blood vessel.

Aizawa teaches in column 18, lines 9-15, and lines 18-28, that in the practice of the Aizawa's photodynamic therapy, the laser beam irradiation is carried out from the tip end of quartz fiber bundle after the administration of the photosensitive tetrapyrrole compound and the irradiation of the laser beam can be done by contacting the tip end of the quartz fiber bundle with the atherosclerotic lesion or by applying the end tip to the surface lesion from a working distance of 5 mm, and that the treatment with the photosensitive compound may be done in one of the two approaches of the Aiawa's proposals by treating with intravascular catheterization, where the specific fluorescence is observed by application of the laser beam through the intravascularly interposed catheter containing the quartz fiber bundle therein directly to the vascular inside wall of the arterial vessel to determine correctly atherosclerotic lesion so that direct treatment of the lesion can be done.

In addition, Aizawa column 20, lines 3 to 48 teaches that the test apparatus as used includes a catheter of 2.1 mm diameter and the quartz fiber bundle of 300 microns in core diameter which is introduced through the intravascularly inserted catheter

(inferred fro the disclosure to effect the necessary irradiation of the laser beam), that the fluorescent photosensistive compound as intravenously administered and accumulated selectively in the atherosclerotic lesion is measured by scanning the vascular intima with the laser beam. Subsequently, the compound was administered and afterwards, the photodynamic therapy treatment was carried out by direct application of the laser beam to the lesion at a laser fluence of 50 J/cm^2.

Aizawa discloses intravascular catherization of a quartz fiber bundle to pass a laser beam therethrough and to irradiate the lesion with the laser beam. However, Aizawa merely teaches intravascular catheterization of the quartz fiber bundle for passage of a laser beam and for intravascular laser irradiation of the atherosclerotic lesion, but Aizawa fails to teach or suggest treating the atherosclerotic lesion just treated by an angioplasty procedure.

The Examiner summarizes these teachings of Aizawa e.g. cols. 18 and 20 in the first paragraph at page 7 of the first Office Action, by his saying that Aizawa also teaches the use of NPe6 during the intravascular catheterization procedure, wherein NPe6 is administered locally to the atherosclerotic lesion of interest in the intima of the blood vessel and subsequently the region is exposed to laser beam to provide a therapeutic effect.

In short, it must be interpreted that the Aizawa's teachings are limited to the intravascular introduction of the laser-emitting quartz fiber bundle through a catheter as intravascularly inserted and the use of NPe6 as the photosentizer to be used for the photodynamic therapy of atherosclerosis as induced in the mammalian blood vessel. The teachings of Aizawa are not be extended to any teaching with respect of the

problem of inhibition or prevention of the restenosis in question in the present application.

Thus, Aizawa is entirely silent on the problem of treating the restenosis of a blood vessel which would be inducible after an angioplasty procedure such as is discussed in column 1 of Narciso, and thus Aizawa provides absolutely no suggestion to motivate one of ordinary skill in the art to combine the Aizawa's teachings with the teachings of Narciso, contrary to the Examiner's allegations.

Turning to Narciso, it is clear that claim 1 and claim 4 of Narciso is also directed to a method for treatment of atherosclerosis.

The claim 4 (Narciso) and its counterpart in column 1, line 61 to column 2, line 4 of the specification, reads as follows:

> "A method for treatment of atherosclerosis comprising the steps of:
>
> widening the lumen of a vessel that has narrowed due to accumulation of atheromatous plaque; and
>
> blocking the growth factor-binding sites on the atherosclerotic smooth muscle cells injured during the widening step, until growth factor is no longer released from the platelets in the vicinity of the injured cells."

In the Narciso method, the step of widening the lumen of a vessel having narrowed due to the accumulation of an atheromatous plaque is carried out by the angioplasty or atherectomy procedure such as PTCA or PTA (see Narciso Abstract and column 1, lines 24-29) for the removal of stenosis, which always can give gross damage or injury to the vessel wall or the intimal surface of the vessel (see column 3, lines 50-58), resulting in that a series of the biological reactions can be involved thereby,

including the migration of smooth muscle cells (SMC) into the intima, the release of platelet-derived growth factors from platelets and the resultant stimulation of rapid SMC proliferation and so on, as well as the restenosis as thus invoked (see column 1, lines 36-56 and column 3, line 50 to column 4, line 21).

In the Narciso method, in a subsequent step, Narciso blocks the growth factor-binding sites of the SMC cells which were injured during the first widening step (namely, the intervention procedure such as the angioplasty treatment) until the growth factors are no longer released from the platelets in the vicinity of the injured cells (see e.g. claims 5, 6, 7 and 8). This blocking step is accomplished by introducing or administering, in the region of the vessel subject to the angioplasty widening step, a photosensitizer, which can accumulate in the atherosclerosis plaque and in the injured SMC cells, so that the photosensitizer as administered and accumulated, can block the sites of the injured SMC cells by binding thereto. The photosensitizer absorbed by the SMC cells render the attached and released growth factors ineffective (see column 2, lines 6-45).

The administration of the photosensitizer may be done either before the vessel lumen-widening step or after the widening step. The administration of the photosensitizer must be repeated by re-administration of the photosensitizer several times for a period of about 5 to 18 days. This time period s necessary to allow for the release of the growth factors from platelets to terminate and to allow for the cessation of SMC proliferation (see Abstract and columns 2, 3, 4).

In the Narciso method, the photosensitizer administered during the blocking step will accumulate in the SMC cells and act as "a competative inhibitor" to block the growth

factor from binding to the growth-binding sites of the injured SMC cells, thus preventing the SMC cells from getting "switched on" by the growth factors, which would otherwise cause rapid SMC proliferation (see Narciso column 4, lines 58-66).

In the Narciso method, it is only after the last administration of the photosensitizer that the photodynamic therapy procedure is conducted in order to make the photo-activation of the photosensitizer by laser irradiation and to achieve the lysis of the atherosclerotic plaque and the injured SMC cells, thereby minimizing or inhibiting the occurrence of restenosis (see Narciso column 2, lines 2-5 and lines 28-45 as well as claim 1 and claim 10-14).

The Narciso disclosure makes it clear that its method is successful only when the method includes the repetition of the re-administration of the appropriate photosensitizer several times for a period of at least about 5 days (see claim 1), followed by effecting the photodynamic procedure after the last administration of the photosensitizer, in order to achieve the intended purpose of preventing the restenosis of the blood vessel which would be inducible after the angioplasty procedure.

Accordingly, it is clear that the Examiner's allegations in the second and third paragraphs of the first Office Action are inaccurate which say:

> "Narciso teaches that photodynnamic theapy is also effective during PCTA procedure to limit restenosis of a blood vessel intima subject to a smooth cell proliferation (see abstract). Narciso specifically explains that the use of a photodynamic agent can be during, before or after a PCTA procedure (see col 2, line 6-65). Narciso also suggests Npe6 to be a suitable photosensitizer for such treatment (see col 7, table 1, under class Phorobides). Since Narciso teaches

the use of photodynamic therapy during a PCTA procedure, all method steps of the instant claims are also inherently disclosed.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to use Npe6 of Aizawa during the PCTA procedure of Narciso".

In this regard, it should be emphasized that NPe6 was used by Aizawa to act merely as the photosensitizer to liberate the cytotoxic singlet oxygen and to kill the SMC cells present in the atheroslclerotic lesion or plaque, whereas NPe6 is used by Narciso in the vascular lumen-widening step (namely, the PTCA procedure) and during the blocking step of the Narciso method is to act in a different way as the competitive inhibitor against the growth factors which will bind to the growth factor-binding sites of the injured SMC cells.

On the other hand, in the present method according to claim 3 (Currently Amended), it is simply required that a single administration of NPe6 at a dosage of 0.1 to 5 mg/kg is conducted only one time before or after effecting the angioplasty treatment, and that the laser irradiation is done at a significantly reduced laser fluence of 1 to 10 J/cm^2 to the NPe6-containing inner wall of the blood vessel at the angioplasty-dilated site, by means of the inflated balloon catheter as recited in claim 3 (Currently Amended), whereby the prevention or inhibition of the restenosis can be achieved successfully, which is entirely unpredictable and unexpectable from Aizawa and Narciso.

Thus, it is clear that Aizawa only teaches the use of NPe6 purely for the purpose of effecting the PDT of the atherosclerosis lesion in a manner such that NPe6 is administered and is allowed to accumulate selectively in the lesion and then photo-activated and excited by the intravascular irradiation of a laser light through the end tip

of the quartz fiber bundle as interposed within the intravascularly inserted catheter, so that NPe6 so photo-excited can produce the cytotoxic singlet oxygen and the cytotoxic effect on the atherosclerosis lesion to regress the lesion (see column 1, lines 9-17 of Aizawa). Aizawa is not concerned with and in no way teaches how to use NPe6 to treat the problem of a restenosis of the blood vessel which would be inducible due to the rapid SMC proliferation invoked after the angioplasty procedure.

Contrary to the Examiner's allegation (see second paragraph at page 7 of the first Office Action), it is clear that Narciso does not teach that the PDT procedure is also effective during PCTA procedure to limit restenosis of the blood vessel intima subject to SMC proliferation. Clearly, in fact, Narciso teaches that, in order to limit such restenosis of the blood vessel having received the PCTA procedure or any other angioplasty treatment, a photodynamic photosensitive agent is absolutely required to be re-administered several times during a period of at least 5 days after the PCTA procedure to maintain the photosensitizer concentration level in the atherosclerotic lesion or plaque and SMC cells, which photosensitizer is necessary to block the growth factor-binding sites of the injured SMC cells, with it acting as a competitive inhibitor against the growth factors which can be liberated from platelets through the series of the biological reaction mechanisms invoked by the PCTA procedure.

In fact, Narciso also teaches that the re-administration of the photosensitizer is required to be repeated several times and to be continued until the release of the growth factors from platelets no longer takes place and thus the elimination of occurance of rapid SMC proliferation (see Narciso Abstract and columns 2, 3 and 4), and that the PDT procedure of the lesion is commenced after the last administration of

the photosensitizer subsequent to the repeated re-administration of the photosensitizer.

In conclusion, clearly, neither Aizawa nor Narciso teaches that the restenosis of the blood vessel which is inducible after the angioplasty procedure can be successfully inhibited using a single administration of NPe6 at a significantly reduced dosage of 0.1-5 mg/kg immediately after the angioplasty procedure and by effecting the intravascular irradiation of laser light of 664 nm at a significantly reduced laser fluence of 1 - 10 J/cm^2 by means of the completely inflated balloon of the intravascularly inserted balloon catheter with the co-current complete interception of the blood stream flowing between the completely inflated balloon of the catheter and the inner wall side of the blood vessel, in accordance with claim 3 (Currently Amended).

The combination of the technical features or technical elements as recited in claim 3 (Currently Amended) is clearly unpredictable from Aizawa and Narciso, either alone or in combination. That the inhibition of a restenosis of the blood vessel inducible after the angioplasty procedure can be achieved with success according to the claimed method claim 3 (Currently Amended) of the present application is entirely unexpectable by one of ordinary skill in the art from the teachings of Aizawa and Narciso.

The fact that the inhibition of a restenosis of the blood vessel inducible after the angioplasty procedure can be achieved with success according to the claimed method of claim 3 (Currently Amended) which includes the combination of the technical features or elements as recited in claim 3 (Currently Amended) that are certainly unpredictable by one of ordinary skill in the art, from Aizawa individually or in combination with Narciso.